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Cytogenetic and Molecular Analysis in Trisomy 12p

Todd L. Allen, Arthur R. Brothman, John C. Carey, and Phillip F. Chance

Division of Medical Genetics, Department of Pediatrics, University of Utah Medical Center, Salt Lake City, Utah (T.L.A., A.R.B., J.C.C.); Division of Neurology, The Children's Hospital of Philadelphia (P.F.C.); Departments of Neurology and Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania (P.F.C.)

We studied a male patient with de novo pure trisomy 12p syndrome by molecular analysis and fluorescence in situ hybridization (FISH) with markers from chromosome 12. G-banding studies demonstrated a 46,XY, 22p+ karyotype and the banding pattern and clinical findings suggested that the extra chromosomal material was derived from 12p. Trisomy 12p was confirmed by dosage analysis with chromosome 12p markers and FISH analysis with a whole chromosome 12 paint. The de novo re-arranged chromosome was of paternal origin.

A comparison of the clinical and cytogenetic findings in this patient was made with previously described cases of trisomy 12p. We propose a classification system for 12p trisomy in order to better characterize the correlative relationships between specific cytogenetic constitution and phenotype.

KEY WORDS: trisomy 12p syndrome, fluorescence in situ hybridization, restriction fragment length polymorphism, cytogenetics, gene dosage, dysmorphic syndrome

INTRODUCTION

Since the initial characterization of the 12p trisomy syndrome [Uchida and Lin, 1973] 32 additional cases have been reported. Most of these (27/33) have resulted from balanced parental translocations, while the remaining six cases were of de novo origin. Three de novo cases involve mosaicism in which the extra 12p arm exists as a marker chromosome [Guerrini et al., 1990; Karki et al.,1990; Kondo et al., 1979] and another exhibits a derivative chromosome 8 and an isochromosome 12p [Rivera et al., 1987]. We report on a patient with partial trisomy 12p, suggested by clinical examination and confirmed by fluorescence in situ hybridization studies (FISH) and molecular analysis with probes specific to chromosome 12. Since no phenotypic abnormalities have been associated with the p-terminal regions of acrocentric chromosomes, this patient, in comparison with most patients with trisomy 12p, is presented as a phenotypically pure description of this syndrome.

In 1981, Stengel-Rutkowski et al. [1981] reviewed 23 cases of trisomy 12p, including two new cases of their own. Their review categorized the cases according to four types of trisomy: 1) partial trisomy 12p, 2) complete trisomy 12p with additional trisomy or monosomy of the short arm of an acrocentric chromosome, 3) complete 12p trisomy with an additional trisomy or monosomy of the terminal region of a non-acrocentric chromosome, and 4) complete trisomy 12p. This classification did not include cases with mosaicism for 12p trisomy.

The existence of cases with mosaicism [Kondo et al., 1979; Savary et al., 1977; Guerrini et al., 1990; Karki et al., 1990] prompted us to re-examine the classification of trisomy 12p. Our analysis expands the classification of Stengel-Rutkowski et al. [1981] by including mosaicism. We propose a classification which is based on the extent of 12p trisomy, the presence of mosaicism and the involvement of other chromosomal regions besides chromosome 12p. This new classification assists in the categorization of cases with trisomy 12p and serves to explore possible relationships between specific chromosomal constitutions and phenotypes.

CLINICAL REPORT

The male patient was born to a 29-year-old gravida 2, para 1-0-0-1 mother after a 40-week gestation to nonconsanguineous parents. There was a previous maternal half sib with no abnormalities. Maternal glycosuria occurred during the third trimester and required no treatment. There was cephalo-pelvic disproportion and forceps delivery was required. Birthweight was 4.0 kg (98th centile) and length was 54.6 cm (98th centile). The patient had postnatal jaundice requiring no treatment and was discharged home at age 3 days.

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Address reprint requests to Dr. Phillip F. Chance, Neurogenetics Laboratory, 516 Abramson Pediatric Research Center, The Children's Hospital of Philadelphia, 34th and Civic Center Boulevard, Philadelphia, PA 19104.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

At age 15 months the patient was hypotonic and had global developmental delay manifested by an inability to crawl, sit, or roll over. There was a history of seizure-like episodes of extensor rigidity. Craniofacial abnormalities including hypertelorism, epicanthus, broad protruding lower lip, and micrognathia were noted.

Chromosome analysis by Giemsa banding demonstrated a 46, XY, +12, der (12;22)(p10;q10) karotype, with the extra material attached distally to 22p having a banding pattern resembling 12p. Parental karyotypes were normal. The banding pattern of the extra material, in combination with physical findings resembling the 12p tetrasomic Pallister-Killian syndrome [Killian et al., 1981; Pallister et al., 1977], led to a provisional diagnosis of trisomy 12p. The patient's partial karyotype is shown in Figure 1.

At age 9 years the patient (shown in Fig. 2) had global developmental delay and generalized hypotonia. He could walk only with assistance, and vocabulary was limited to the words "mama" and "papa." Physical examination showed a weight of 32.3 kg (80th centile), height of 134.6 cm (50th centile), and occipital-frontal circumference of 53.9 cm (80th centile). He also had a mildly prominent forehead with a narrow bifrontal region, wrinkling of the glabella, normal slant of the palpebral tissues, bilateral epicanthus, and hypertelorism. Inner canthal distance was 3.2 cm (75th centile), and interpupillary distance measured 5.9 cm (97th centile). Ears were normal in size and placement, having small uplifted lobules, and prominent antitragii. A low nasal root with poorly defined bridge, short upturned nose, prominent protruding lower lip, and widely spaced teeth accompanied by a class III malocclusion and generally flat face were present. Increased ridges of the gums and a bifid uvula were also noted. There was tapering of all digits and short fifth fingers with clinodactyly. The palm and the third digit of both hands measured at the 50th centile. Hallux valgus and general valgus of all toes was present and was accompanied by bilateral pes planus and pronation of the right foot. Bilateral accessory nipples and a mild chordee were present.

MATERIALS AND METHODS

Molecular Analysis and Gene Dosage Determination

Genomic DNA probes localized to chromosome 12p and encoding loci for von Willebrand factor [pSV2, Sadler et al., 1986], proline rich protein [pPRP1, Chaffanet et al., 1995], alpha 2 macroglobulin [pHLA2M1, Poller et al., 1992], and D12S2 [p12-16, Balazs et al., 1984] were studied. Marker D12S4 [probe p9F11, Blumenfeld et al., 1995] was used as a control for chromosome 12q. The order and approximate cytogenetic localizations of these markers were determined according to published maps [O'Connell et al., 1987; NIH/CEPH Collaborative Mapping Group, 1992; Blumenfeld et al., 1995; Chaffanet et al., 1995] and are depicted in Figure 3. Under a protocol of informed consent (University of Utah Medical Center), 30 ml of blood was collected by venipuncture from the patient and parents. Lymphoblastoid cell lines were established according to Neitzel [1986]. Methods of restriction enzyme digestion, gel electrophoresis, Southern transfer, and molecular hybridization have been previously described by Chance et al. [1992]. Five micrograms of DNA from the subjects and the unrelated control were digested overnight, using the appropriate restriction enzymes for detection of restriction fragment length polymor-

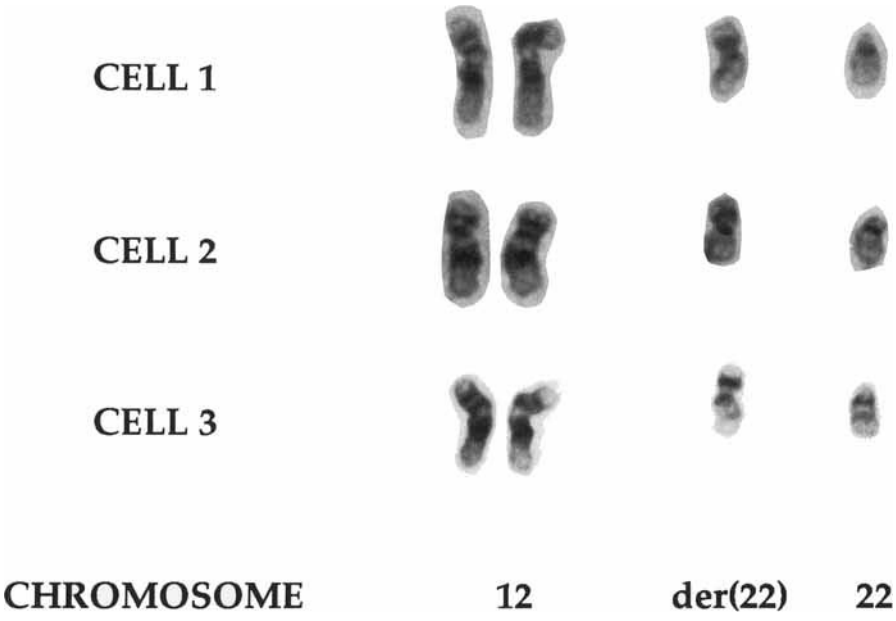

Fig. 1. Partial karyotype of patient showing chromosomes 12 and 22, from 3 metaphase cell preparations (approximately 500 band level).

Fig. 2. Photograph of patient at age 9 years.

phisms (RFLPs). Gene copy number was estimated by visual assessment of polymorphic bands on autoradiograms and by densitometric analysis (PhosphorImager, Molecular Dynamics) and comparison to a control marker, an 800 bp fragment from exon 1 of the NF1 gene [Cawthon et al., 1990].

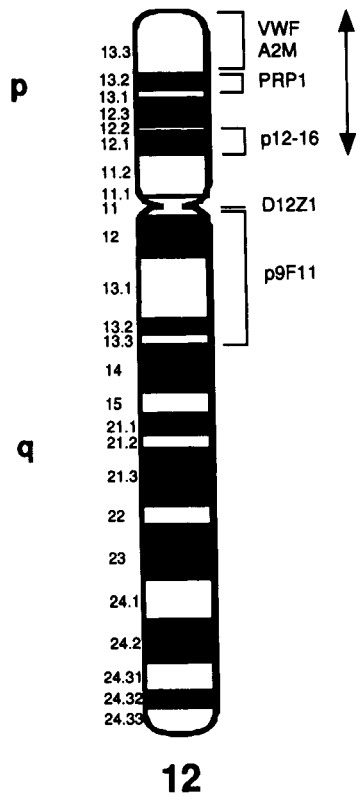

Fig. 3. Idiogram of chromosome 12 showing order and approximate cytogenetic map location of markers as determined from published reports (O'Connell et al., 1987; NIH/CEPH Collaborative Mapping Group, 1992; Blumenfeld et al., 1995; Chaffanet et al., 1995). The trisomic region in the patient is shown between arrowheads.

Fluorescence In Situ Hybridization (FISH) Analysis With a Chromosome 12-Specific Centromeric Probe

Metaphase chromosome spreads were prepared using routine methods following 72 hour culture of phytohemaglutinin-stimulated peripheral blood in RPMI medium supplemented with 20% fetal bovine serum. Following colcemid block, hypotonic treatment, and Carnoy's fixation, slides were prepared and subjected to G-banding using trypsin and Wright stain or stored at room temperature for FISH analysis.

A biotinylated centromeric probe for chromosome 12 (D12Z1) was purchased from Oncor (Gaithersburg, MD). The probe was labeled by nick-translation with Bio-11-dUTP. The method of Pinkel et al. [1986] was carried out with slight modifications. Slides were immersed in 70% formamide/2X SSC (pH 7.0) for 2 minutes to denature; 10 μl of the hybridization mix containing 65% formamide, 2X SSC, 500 μg/ml salmon sperm DNA, 5% dextran sulfate, and 0.5 μg/ml probe was heated at 70°C for 5 minutes and applied to each slide. Hybridization was carried out overnight at 37°C in a humid chamber. Post-hybridization washes were accomplished in 65% formamide at 43°C for 20 minutes, followed by two washes in 2X SSC (pH7.0) at 37°C for 4 minutes each. The slides were transferred to PN buffer (0.1 M NaH_2PO_4 and 0.1 M Na_2HPO_4 to pH 8.0, 0.1% NP-40) at room temperature.

Detection of probe was accomplished by applying FITC-labeled (fluorescein isothiocyanate) avidin (5 μg/ml in PMN buffer: PN buffer + 5% Carnation non fat dry milk). Amplification was achieved by applying biotinylated anti-avidin followed by another layer of FITC-avidin. The chromosomes were counterstained using propidium iodide (0.5 μg/ml) in an antifade solution [Johnson et al., 1981]. Twenty metaphase cells were examined.

Hybridization With a Whole Chromosome 12 Library

A labeled whole chromosome 12-specific DNA library (whole chromosome "paint"; WCP) was provided by Imagenetics (Naperville, IL). The hybridization procedure employed was essentially the same as outlined above for the centromeric probe with the following changes: 1) hybridization mix was first heated for 5 minutes at 70°C , and incubated at 37°C for 1 hour, before incubation on the slide, 2) total human genomic DNA was used to block hybridization of non-specific DNA. Post-hybridization washes were done in three changes of 50% formamide/2X SSC, followed by a wash in 2X SSC and PN buffer. All washes were performed at 45°C for 15 minutes each. Twenty metaphase cells were examined using a blue-filtered BH2-DMB dichromic mirror cube on an Olympus BH2 microscope. Kodak Ektachrome 400 Daylight film was used for the photomicrographs.

RESULTS

Molecular Analysis

As shown in Figure 4 increased gene dosage is seen for PRP1 as evidenced by a 2 to 1 ratio (6.1 kb to 6.3 kb

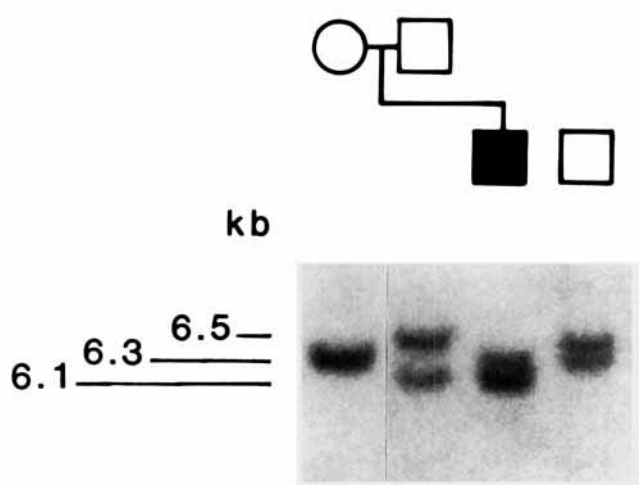

Fig. 4. Autoradiograph of DNA from mother, father, patient, and control subject digested with *Eco*RI and probed with pPRP. A dosage effect resulting from trisomy is seen in the patient for the 6.1 and 3.5 kb fragments.

fragments) in the patient, suggesting a trisomic copy number at this locus. The patient inherited a single 6.3 kb fragment from his mother and two copies of the 6.1 kb fragment from his father, indicating that the origin of the de novo trisomy for 12p is paternal. At the A2M locus the patient has increased hybridization intensity of a 2.5 kb fragment relative to a 2.7 kb fragment suggesting that three copies of this locus are present (data not given). Gene copy number for the VWF (probe pSV2) locus and D12S2 (probe p12-16) locus was determined by quantitation of band density and comparison with a control marker (NF1 gene fragment). Three copies of the VWF and D12S2 loci were detected (data not shown). D12S2 has been localized to chromosome 12p12.1-p12.2, suggesting that the breakpoint is proximal to band p12.1. Similarly, analysis with marker D12S4 (probe p9F11) which maps to the proximal long arm (12q12-13.3) detected two copies in the patient's DNA. Figure 3 depicts the approximate region of 12p which is trisomic in the patient.

FISH Analysis

An analysis with hybridization of a whole chromosome paint (WCP) for chromosome 12 to a metaphase preparation of patient chromosomes is depicted in Figure 5. The WCP detects signals from each of three chromosomes with intense hybridization to the two normal chromosome 12 homologs and an additional hybridization signal from the derivative chromosome 22. FISH analysis using the chromosome 12 centromeric marker, D12Z1 detected signals from the two normal homologs, but not from the derivative chromosome 22 (data not shown).

DISCUSSION

Trisomy 12p has been estimated to occur at a rate of 1/50,000 births [Stengel-Rutkowski et al., 1981]. The first reported case [Uchida and Lin, 1973] was initially diagnosed as having Down syndrome, based on presence of mental retardation, hypotonia, flat face, epicanthus, broad nasal bridge, bilateral simian creases, and abnormal dermal patterns. Later, chromosome staining with quinacrine dihydrochloride demonstrated trisomy 12p and monosomy for the distal region chromosome

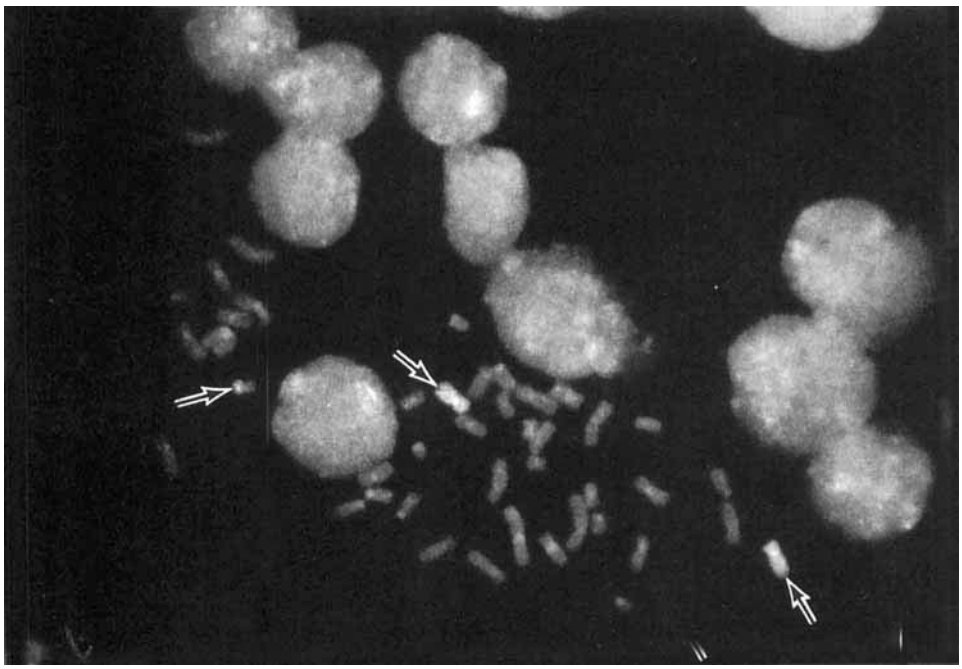

Fig. 5. FISH studies of the patient's chromosomes using a whole chromosome paint (WCP) for chromosome 12. Arrows mark regions of hybridization on the two normal chromosome 12 homologs and on the der (22) chromosome.

TABLE I. Proposed Classification for 12p Trisomy

Category	Pure	Complete	Mosaicism	12q involved
I	Yes	No	0/1	No
II	No	?	2/2	No
III	Yes	Yes	0/12	No
IV	No	Yes	0/13	No
V	No	Yes	2/6	Yes

8p. Comparison of this case to other cases of trisomy 12p shows that additional aneusomies add abnormalities not associated with pure trisomy 12p. Interestingly, in most of reported trisomy 12p cases the breakpoint is in band 12p11, while in six cases breakpoints were reported in the 12q and five are uncharacterized.

For purposes of comparison, cases of trisomy 12p can be subdivided into five categories (Table I) based on the extent of the 12p trisomy and the presence of other chromosomal aneusomies. We define "complete" trisomy as having a duplication region of 12p11 or 12p12-12pter, and "pure" as having no other aneusomy or additional aneusomies of only the pter regions of non-acrocentric chromosomes, and not involving mosaicism. Category I will be designated as a partial pure trisomy of 12p with a duplication point distal to 12p11 and not involving any other chromosome. Such a scenario includes the case reported by Tayel et al. [1989], which is the only case to involve a terminal duplication of 12p attached to a normal chromosome 12, and may represent a more benign presentation of trisomy 12p. This case documents a patient with a measured IQ of 51. This case serves to illustrate the following: 1) breakpoints distal to 12p11 do modify the severity of the retardation and phenotypic presentation, 2) involvement of non-acrocentric chromosomes does affect the clinical phenotype, and 3) there is variability in the phenotypic expression of trisomy 12p likely due variable breakpoint placements.

Category II includes cases of Karki et al. [1990] and Guerrini et al. [1990] which describe 12p trisomies in association with cell-line mosaicism. Category II patients appear to express the same manifestations as those in category III, but with less uniformity as summarized in Table II. Both Karki et al. [1990] and Guer-

TABLE II. Compilation and Comparison of All Trisomy 12p Cases According to the Proposed Classification System*

	I	II		III				IV							V			
Author (see key)	TA	GU1	KA	RA	TR	SR	SR-R	QA	RI	GU3	B-N1	B-N2	B-N3	SR-R	SA	KO	SR1	SR-R
Finding																		
Hypotonia	+	+	+	0	+	+	3/4	+	+	+	+	+	+	2/3	+	+	+	2/2
Feeding difficulties	0	0	0	0	0	0	2	5/5	0	0	0	0	0	3/3	+	0	+	0/0
Neonatal death	–	–	–	–	–	–	0/9	+	–	–	–	–	–	1/7	–	–	+	2/3
Broad/high/prominent forehead	+	+	0	+	+	+	9/9	+	–	+	–	+	+	3/3	0	(+)	+	3/3
Prominent cheeks	–	0	+	+	+	+	6/6	+	+	+	+	+	+	3/4	+	+	+	1/1
Hypertelorism	?	0	+	(+)	+	+	1/1	+	+	+	+	0	+	2/3	+	+	+	3/3
Epicanthus	?	0	+	+	+	+	3/4	+	+	0	+	0	+	3/6	+	+	–	1/2
Flat/broad nasal root	1	+	+	+	+	+	6/7	+	+	0	0	+	+	5/6	+	+	+	3/3
Short nose	+	0	+	+	+	+	9/9	+	+	+	+	+	+	6/6	+	+	0	2/2
Anteverted nares	–	0	+	+	+	+	6/8	+	(+)	+	(+)	(+)	(+)	4/4	+	+	0	2/2
Long philtrum	+	0	+	+	+	+	5/7	+	+	0	+	+	+	4/4	+	+	+	2/2
Everted lip	+	0	+	+	+	–	8/8	+	+	+	+	0	+	5/6	+	+	–	2/2
Downward slanting corners of mouth	+	0	+	(+)	+	+	1/6	(+)	(–)	0	+	+	–	3/4	+	0	–	3/3
Backward slanting ears	+	+	+	+	?	+	4/4	0	+	0	+	–	+	2/3	+	+	+	3/3
Short neck	(–)	0	+	+	+	+	9/9	+	+	0	+	+	+	6/6	+	+	+	2/3
Short/broad hands/feet	0	+	0	+	–	+	3/3	0	0	0	?	?	?	1/2	0	+	+	1/2
Foot deformities	+	+	+	+	+	+	7/7	+	0	+	+	+	–	4	+	+	0	2/2
Other congenital anomalies																		
Hypoplastic heart	–	–	–	–	–	–	0	+	–	–	–	–	–	1	–	–	–	1
Other CHD	0	0	–	–	–	?	2	0	0	0	0	0	0	1	–	–	+	2
Imperforate anus	0	0	0	0	–	+	0	0	0	0	–	–	+	1	+	0	–	0
Cleft/palate bifid uvula	0	+	–	0	+	+	0	0	0	+	0	0	0	1	+	0	–	1
Seizures	0	+	–	–	?	0	+	+	0	+	0	0	0	1	+	+	?	0
Polydactyly	0	0	–	–	–	0	1	0	0	0	0	0	0	0	+	+	0	1
Accessory nipples	0	0	0	0	+	(–)	2	0	+	0	0	0	0	0	0	0	0	0
Clinodactyly	0	0	+	+	5	5	5	+	0	0	+	+	+	3	0	0	5	3
High palate	0	+	+	0	+	+	+	+	0	+	0	0	0	1	0	+	+	1
Abnormal EEG	0	+	+	0	0	0	3	0	0	+	0	0	0	1	0	+	0	0

*TA, Tayel; GU1, Guerrini Case 1; KA, Karki; RA, Ray; TR, this report; SR2, Stengel-Rutkowski Case 2; SR-R, Stengel-Rutkowski Report: Compilation of Category III 12p Trisomies; QA, Qazi; RI, Rivera. 1, anomaly present; 2, anomaly absent; (1) or (2), anomaly present or absent by photograph; 0, no information; ?, indeterminate.

rini et al. [1990] described their patients as having complete 12p trisomy although breakpoints were not specified. We conclude that cell-line mosaicism does affect clinical expression of trisomy 12p. Furthermore, category II mosaic cases are phenotypically distinct from the mosaic patients of Savary et al. [1977] and Kondo et al. [1979]. The trisomic region in these patients included 12q and they present with a much greater frequency of associated malformations such as polydactyly.

Category III includes the present cases and other cases with complete and "pure" 12p trisomy with an additional trisomy or monosomy of the short arm of an acrocentric chromosome. As depicted in Table II, the common physical features of the pure and complete trisomy 12p cases include normal to large birthweight, normal physical development, and severe psychomotor retardation. A prominent forehead with flat faces, hypertelorism, bilateral epicanthus, low nasal root, short upturned nose with anteverted nares, large mouth, prominent protruding lower lip, bifid uvula, micrognathia, and short neck are seen. Supernumerary nipples, tapering and clinodactyly of the digits, pes planus, hallux and metatarsal valgus, and hypotonia are also near constant features. Duration of life of pure cases appears relatively unimpaired at this point, and will probably be comparable to patients with the Down syndrome. Patients have been reported during their 13th and 14th years of life [Kondo et al., 1979; Tayel et al., 1989]. The prognosis for psycho-motor development is poor.

Categories IV and V involve complete 12p trisomy with monosomy or trisomy of non-acrocentric chromosomes other than 12p, or trisomic involvement of 12q, respectively. The phenotypic manifestations commonly found in categories IV and V include turricephaly,upslanting palpebral tissues,exophthalmia, and simian creases. Other findings which are more commonly seen in categories IV and V include cardiac and renal abnormalities, cryptorchidism, and increased space between the first and second toes. The case of Uchida and Lin, [1973] had anomalies of this type, thus leading to the provisional diagnosis of Down syndrome. By our classification system, their case is placed in category IV. These anomalies are likely the result of aneusomy, or gene sequence disruption, for chromosomes other than 12p.

The categorization of trisomy types is not arbitrary. Comparison between the published cases shows subtle but significant differences among the categories of 12p trisomy (Tables I and II). Two abnormalities that have received particular attention are generalized seizure discharges and hypoplastic left heart. Seizures are generally 3 Hz spike and wave discharges, manifested by generalized convulsions, myoclonic jerks, febrile seizures, or clonic spasms as described by Guerrini et al. [1990]. Seizures have been present in all but category I cases of trisomy 12p. Qazi et al. [1981] described a case of hypoplastic left heart and compared this case to two others with the same anomaly [Fryns et al., 1974; Nielsen et al., 1977]. Each case with confirmed hypoplastic left heart involved aneusomy of a non-acrocentric chromosome in addition to trisomy 12p. All cases had early post-natal death. In two other cases (both category III) findings suggestive of cardiac abnormalities were observed, but not confirmed [Biederman et al., 1977; Hansteen et al., 1978]. Cardiac involvement in the above five cases of trisomy 12p may represent a non-random association that bears further investigation.

The widespread application of chromosome-specific DNA libraries and FISH studies including those in patients with de novo duplications will likely result in the identification of additional cases with trisomy 12p [Leana-Cox et al., 1993]. Compared to other human chromosomes, chromosome 12 has fewer precisely localized markers available for diagnostic studies. This relative scarcity limits a better understanding of trisomy 12p syndrome. Further characterization of 12p by markers spanning the entire arm may also uncover loci directly responsible for particular aspects of the observed phenotype, and thus aid in the elucidation of the relationship between specific cytogenetic abnormality and phenotypic consequence.

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